**Citation:**

Yang Q, Botto LD, Erickson JD, Berry RJ, Sambell C, Johansen H, Friedman JM. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. *Circulation.* 2006 Mar 14; 113 (10): 1,335-1,343.

**PubMed ID:** 16534029

**Study Design:**

Population-based cohort study

**Class:**

B - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To examine national stroke mortality data from the United States (US) and Canada, where mandatory fortification has been in place since 1998 and compare the findings with similar data from England and Wales, where fortification is not mandatory, to see if accelerated improvement in stroke mortality occurred in association with folic acid fortification.

**Inclusion Criteria:**

- Adults 40 years of age or older included in the National Center for Health Statistics Multiple Cause Mortality Files of the Centers for Disease Control and Prevention ( CDC)
- Similar data were obtained from the Canadian Mortality Database at Statistics Canada and from the UK Office for National Statistics for England and Wales.

**Exclusion Criteria:**

Adults in aforementioned databases younger than 40 years of age.

**Description of Study Protocol:**

**Recruitment**

Data came from already-established, public access national databases; no recruitment.

**Design**

Population-based cohort study.

**Dietary Intake/Dietary Assessment Methodology**

None stated.

**Intervention**

Folic acid fortification of enriched grain products.

**Statistical Analysis**

- Mortality rates were age-adjusted with 2000 population as standard in the US, 2001 population as standard in Canada and the European standard population in England and Wales
- The researchers computed rates by sex, age group (40 to 49, 50 to 59, 60 to 69 and older than 70 years of age) and in the US, race white or black, the only groups with consistent definitions and large sample size in the National Health and Nutrition Examination Survey [NHANES] data sets)
- To document changes in trends concurrent with flour fortification, the authors used 1998, the year implementation was completed in the US and Canada, as the boundary point and conducted simple segmented log-linear regression of age-adjusted mortality rates in 1990 through 1997 versus 1998 through 2002
    - Testing for a significant difference between the regression lines for the two segments was done by using the T-test
- Authors estimated the annual change in mortality rate before and after 1998 from the slope of the simple segmented log-linear regression
- To estimate how many fewer deaths occurred each year after 1998, the authors used the 1990 to 1997 trend to predict 1998 to 2002 mortality rates and computed the difference between observed and predicted number of deaths
- To evaluate the extent to which changes in known risk factors for stroke could affect mortality rates during the study period, the authors conducted a sensitivity analysis using NHANES data for the US.

**Data Collection Summary:**

- *Timing of measurements:* One-time data collection (using national population-based databases)
- *Dependent variables:* Incidence of stroke
- *Independent variables:* Folic acid fortification of enriched grain products
- *Control variables:* (In sensitivity analyses) researchers controlled for

- Cigarette smoking
- Hypertension
- Diabetes
- Total serum cholesterol levels.

**Description of Actual Data Sample:**

- *Initial N*: Unclear, only rates and percentage given
- *Attrition (final N):* Unclear, only rates and percentage given
- *Age:* 40 years or older
- *Ethnicity:*
  - For US only: white, black
  - Ethnicity/race for other countries not reported
- *Other relevant demographics:* Not applicable
- *Anthropometrics:* Not applicable
- *Location:* US and Canada (compared to England and Wales).

**Summary of Results:**

- In this study the authors used segmented log-linear regression to evaluate trends in stroke-related mortality before and after folic acid fortification in the US and Canada and, as a comparison, during the same period in England and Wales where fortification is not required
- Average blood folate concentrations increased and homocysteine concentrations decreased in the US after fortification. The ongoing decline in stroke mortality observed in the US between 1990 and 1997 accelerated in 1998 to 2002 in nearly all population strata, with an overall change from -0.3% ( 95% CI, -0.7 to 0.08) to -2.9 (95% CI, -3.5 to -2.3) per year (P=0.0005)
- Sensitivity analyses indicate that changes in other major recognized risk factors are unlikely to account for the reduced number of stroke-related deaths in the US. The fall in stroke mortality in Canada averaged -1.0% (95% CI, -1.4 to -0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI, -6.0 to -4.7) per year in 1998 to 2002 ($P \leq 0.0001$)
- In contrast, the decline in stroke mortality in England and Wales did not change significantly between 1990 and 2002
- Sensitivity analysis based on changes in the prevalence of smoking, hypertension, diabetes and serum total cholesterol concentration ≥240mg/dL in the US during the period of study predicted a 0.1% increase (2.5th to 97.5th percentile, 5.2% decline to 5.3% increase) in stroke mortality after 1998. A 9.3% decline actually was observed
- In the US, the estimated annual percent decline in stroke-related mortality rates among whites in all age and sex groups was ≤1.0%, with one exception, before fortification and increased to ≥2.7% after fortification. A similar effect was seen among blacks, with the annual decline increasing from 1.4% among men and 0.7% among women before fortification to 2.9% among men and 2.7% among women after fortification. These percentages translate into approximately 12,900 fewer stroke deaths per year among people ≥40 years of age in the US than if the trend established in 1990 to 1997 had continued without change.

**Author Conclusion:**

The improvement in stroke mortality observed after folic acid fortification in the US and Canada, but not in England and Wales is consistent with the hypothesis that folic acid fortification helps to reduce deaths from stroke.

***Reviewer Comments:***

*No funding source given.*

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***Research Design and Implementation Criteria Checklist: Primary Research***

| **Relevance Questions** | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

| **Validity Questions** | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |

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| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | ??? |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | Yes |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | ??? |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | N/A |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | No |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | No |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | N/A |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | N/A |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | N/A |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | ??? |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | Yes |

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|---|---|---|
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | Yes |
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | Yes |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | No |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | Yes |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | N/A |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | N/A |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | Yes |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | ??? |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |

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|---|---|---|
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | N/A |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | ??? |
| 8.6. | Was clinical significance as well as statistical significance reported? | Yes |
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | N/A |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |
| 9.1. | Is there a discussion of findings? | Yes |
| 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | Yes |
| 10.1. | Were sources of funding and investigators' affiliations described? | No |
| 10.2. | Was the study free from apparent conflict of interest? | Yes |